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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,676	03/21/2002	Klaus Ducker	MERCK 2393	4823

23599 7590 05/20/2004

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,676	DUCKER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 6-9* is/are rejected.

7)☒ Claim(s) *2,3 and 5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-26-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11 are currently pending and are present for examination. Claims 1-9 are now under consideration. Claims 10-11 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-9 in Paper filed on 2-17-04 is acknowledged. The traversal is on the ground(s) that coexamination of all of Groups I-III would not be an undue burden to the Examiner. This is not found persuasive because while the searches for the three groups may overlap, they are not coextensive. The search for Groups I and II would each require the search of subclasses unnecessary for the search of elected Group I. For example, search of Group I would require search of subclass 435/200 and search of Group II would require search of subclass 530/387.9

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper filed on 2-17-04.

Rejoinder of restricted inventions

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim

will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. **Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112.** Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. **Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined.** See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to rejoin, in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent PCT Application.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 recites the phrase "the sequence" in line 3 as a single word. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 8 and claims 2-3, 5-7 and 9 all of which depend from claims 1, 4, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1, 4 and 8 recite the phrase "selected from one of the groups consisting of". It is not clear to the Examiner as to what applicants mean by the above phrase as there is only one group in said claims. It appears that applicants meant to recite "selected from the group consisting of.." if this is so amending the claim accordingly would overcome the above rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a full length polypeptide having an amino acid sequence SEQ ID NO:2 encoded by the polynucleotide sequence SEQ ID NO:1, wherein said polypeptide has heparanase enzyme activity and host cells comprising said polynucleotide and a method of making said polypeptide using said polynucleotide, does not reasonably provide enablement for any polypeptide having at least 95% sequence identity with SEQ ID NO:2 or any polypeptide fragments or variants of such polypeptides as well as any polynucleotide that is at least 95% identical to SEQ ID NO:1 or any polynucleotide encoding a polypeptide that has at least 95% sequence identity with SEQ ID NO:2 or any polynucleotide or a fragment of at least 15 nucleotides that simply hybridizes under stringent conditions to SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 4, 6-9 are so broad as to encompass any polypeptide or fragments or variants of such polypeptides as well as any polynucleotide that is at least 95% identical to SEQ ID NO:1 or any polynucleotide encoding a polypeptide that has at least 95% sequence identity with SEQ ID NO:2 or any polynucleotide or a fragment of at least 15 nucleotides that simply hybridizes under stringent conditions to SEQ ID NO:1. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides and polynucleotides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of a single heparanase. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with an undefined function/activity. The specification is limited to teaching the use of SEQ ID NO: 2 as a heparanase but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue

experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any heparanase with 90% identity to the enzymes of SEQ ID NOS:6 and 8 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting heparanase activity; (B) the general tolerance of heparanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or a nucleotide residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including heparanases with an enormous number of amino acid modifications of SEQ ID NOS: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient

guidance, determination of heparanase polypeptides and polynucleotides encoding the same is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 4 is directed to a genus of polynucleotides that are 95% identical to SEQ ID NO:1 or encodes a protein that is 95% identical to SEQ ID NO:2 or polynucleotides that simply hybridize to SEQ ID NO:1 under stringent conditions.

The specification does not contain any disclosure of the function of all polynucleotide sequences that are 95% identical to SEQ ID NO:1 or that of the polypeptide encoded by the same or polynucleotides that simply hybridize to SEQ ID NO:1 under stringent conditions. The genus that comprise these above polynucleotides is a large variable genus with the potentiality of encoding many different proteins. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 6-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 6-9 are directed to polypeptides that are 95% identical to SEQ ID NO:2 and variants and fragments corresponding sequence of SEQ ID NO:2. Claims 1, 6-9 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2 and fragments of SEQ ID NO:2 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 as a heparanase has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the function of all the polypeptide sequences derived from SEQ ID NO:2, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of functions and with the potentiality of generating many different antibodies. Therefore many functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 4, 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Pecker (a) et al. (WO 200100643-A2, 1-4-2001, priority date 6-25-1999) or Pecker (b) et al. (US 5,968,822 10-19-1999) or Nakajima et al. (US 6,461,848, 10-8-2002). This rejection is based upon the public availability of a printed publication. Claims 1, 4, 6-9 of the instant application are drawn to polypeptide comprising a polypeptide that is at least 95% identical with SEQ ID NO:2 or drawn to a polypeptide having at least 95% sequence identity with SEQ ID NO:2 or a fragments and variants and fusion proteins of the same and polynucleotides comprising a polynucleotide that is at least 95% identical to SEQ ID NO:1 or polynucleotide having a sequence identity of 95% with SEQ ID NO:1, or a polynucleotide or a fragment of the same which can hybridize with

SEQ ID NO:1 under stringent conditions and host cells comprising such polynucleotides and a method of making the polypeptide using such host cells.

Pecker (a)et al. disclose a polynucleotide that is more than 95% identical with SEQ ID NO :1 encoding a polypeptide that is more than 95% identical to SEQ ID NO:2, and capable of hybridizing with SEQ ID NO:1 under stringent conditions, vectors and host cells comprising such polynucleotides and method of making such polypeptides using such polynucleotides (see enclosed sequence alignments). Therefore Pecker et al. anticipate claims 1, 4, 6-9 as written.

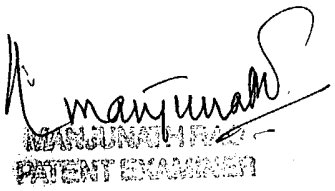
Pecker (b) et al. and Nakajima et al. disclose a variant polynucleotide which encodes a variant heparanase of SEQ ID NO:2 as well as vectors and host cells comprising such variant polynucleotides and fusion proteins. Since there is no limitation placed on the number of changes that can be present in the polynucleotide sequence, SEQ ID NO:1, for encoding a variant polypeptide heparanase, claims 1, 4, 6-9 read on the polynucleotide and polypeptide sequence disclosed by Pecker(b)et al. and Nakajima et al. Thus Pecker(b)et al. and Nakajima et al. anticipate claims 1, 4, 6-9 of this application as written.

Claims 2, 3, 5 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 1, 4, 6-9 are rejected and claims 2, 3, 5 are objected..

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
May 18, 2004